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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/780,294	DOW ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 6/7/2007.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Applicants' response of April 2, 2007, to the non-final action dated January 4, 2007 has been entered. Claims 1-22 are pending in the application. Claims 1 and 10-13 have been amended. No claims were cancelled or newly added. Claims 1-22 are currently under examination.

New Claim Rejections - 35 USC § 112- Second Paragraph

Applicants' claim amendments have necessitated the following new grounds of rejection. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 depends from claim 1 and is directed to an oligonucleotide that "is in the range of 10 to 100 base pairs in length". Thus, the claim includes an oligonucleotide having 10 base pairs in length. However, base claim 1 encompasses oligonucleotides that are "from more than 10 to about 500 nucleotides in length", thus excluding an oligonucleotide of 10 nucleotides in length. Therefore the oligonucleotide length of claim 12 conflicts with the limitation of the base claim and thus renders the claim indefinite.

Response to Claim Rejections - 35 USC § 112 – Written Description

Claims 1-22 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The rejection set forth on pp. 2-4 of the previous office action dated January 4, 2007 is maintained for reasons of record. It should be noted that the claim numbering on page 2 of the previous office action is clearly in error (as it includes claims

29-31 that are not part of the instant application), and the rejection should have included all the claims, i.e. claims 1-22 inclusively.

Applicants traverse the rejection, arguing that the rejection shows there is a misunderstanding of what is necessary in the form of representative examples, as a skilled person would clearly understand the oligonucleotide to be one which contains any sequence as long as it does not contain a CpG dinucleotide (where the "p" in CpG simply represents a phosphate moiety present between the cytosine and guanine residues). Additionally arguing that these non-CpG dinucleotide sequences are the structural features, or specific characteristics, which define the oligonucleotides of the claimed invention, and the oligonucleotides featured in the claims are clearly not described only by a functional characteristic as alleged in the statement of the rejection. Applicants further state that SEQ ID NOS: 2-5 all produce the immune response as featured in the claims, when used with a liposome delivery vehicle, and cite MPEP 2163IIA.3 to indicated precedent for a single representative species to adequately support a genus.

Applicants' arguments have been fully considered, but are not found persuasive, as the issues indicated in the previous office action did not arise from a misunderstanding of what a CpG motif represents. The office action noted that the instant claims embrace an enormous number of oligonucleotides lacking CpG motifs, constituting a genus, and that the specification fails to disclose a representative number of the numerous ribonucleotides, deoxyribonucleotides or chemically modified oligonucleotides of any size or sequence composition, lacking CpG motifs, that would further be able to elicit a therapeutic systemic, non-antigen-specific immune response. Applicants' claim amendments to limit the oligonucleotide lengths to about 500 nucleotides fails to obviate the ground for rejection. The instant specification does not describe the structure or functional nature of the numerous oligonucleotides, other than a single distinct sequence of a 25mer, 50mer, 75mer and a 100mer. The specification is further silent on the specific characteristics, or sequence motifs of any non-CpG oligonucleotides, that may contribute to a therapeutic immune response. The claims thus embrace a claimed genus that encompasses oligonucleotide sequences yet to be discovered.

Regarding the reference to MPEP 2163IIA.3, it is clear that from the case law quoted, that the invention must have a corresponding written description that is so specific as to lead one of ordinary skill in the art to the class of compound. In the instant case, any oligonucleotide of

ranging in size from 10 to about 500 nucleotides in length that lacks a CpG motif is embraced by the claims. However, any such oligonucleotide is not necessarily capable of eliciting a systemic, non-antigen specific therapeutic response in a mammal, as said response is further dependent on specific sequences that so far remain undefined and are not apparent from the four oligonucleotides disclosed in the instant specification. Moreover, MPEP 2163 states: [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

The previous office action also noted that the instant claims additionally embrace ribonucleotides and chemically modified oligonucleotides. Applicants argue that ribonucleotides merely introduce the possibility of a uracil residue and that there is no basis to require an adequate written description of a chemically modified oligonucleotides when the claims are not limited to such a feature. In response, it should be noted that the sequences responsible for eliciting a systemic therapeutic immune response remain undefined for deoxyribonucleotides, as well as ribonucleotides and chemically modified oligonucleotides. Further, while the claims are not limited to chemically modified oligonucleotides, they do not exclude said oligonucleotides.

Thus, the previous rejection is maintained for claims 1-22 for reasons of record, and the foregoing discussion.

Response to Claim Rejections - 35 USC § 112 - Lack of Enablement

Claims 1-22 stand rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The rejection set forth on pp. 4-8 of the previous office action dated January 4, 2007 is maintained for reasons of record.

Applicants traverse the rejection, arguing that the rejection appears to erroneously focus on "a treatment of tumors in a mammal", which is not a limitation of any pending claim. So while eliciting a systemic, non-antigen-specific immune response in a mammal with a composition of the invention may include the generation of an immune response that is beneficial in the treatment of tumors in the mammal, there is no basis to require specific

enablement of "treating tumors" when the claims do not recite such a limitation, and that the rejection erroneously attempts to shift the focus from the immune response recited in the claims to the issue of reducing tumor size in a mammal. Applicants further argue that the Examples presented in the specification cannot be attacked or used against the Applicants unless there is an objective reason to doubt the support provided by the Examples; stating that the immune responses in Examples 12-15 correspond to oligonucleotide used in combination with a liposome delivery vehicle.

Applicants' arguments have been fully considered, but are not found persuasive. It is noted that the claims have been examined in view of the as filed specification, and embrace a method for using a composition comprising a liposome delivery vehicle and an oligonucleotide containing no CpG motifs composition in a treatment of tumors in a mammal when administered as a therapeutic vaccine. The specification states: "The above-mentioned method and compositions of the present invention have the advantages of eliciting a systemic, non-antigen specific immune response in a mammal, and more particularly, of eliciting a systemic, anti-viral immune response in a mammal. Additionally, the method and composition of the present invention can elicit a systemic, anti-tumor immune response in a mammal. Such an anti-tumor immune response can result in the reduction of a tumor in the mammal." (paragraph [0015], p. 4). Further, a number of the Examples provided in the disclosure of the invention are directed to assessing the antitumor effects of said oligonucleotides *in vivo*. Therefore, because the claims are directed to therapeutic compositions, it is appropriate to look to the specification to ascertain what the claimed composition is therapeutic for. While the method claims do not recite "therapeutic", the specification makes clear the intended use of the method for treatment of virus infections and tumors. A method of eliciting a systemic, non-antigen specific immune response in a mammal would otherwise be of no benefit, in the absence of providing a treatment. Therefore, examination of the claims with respect to treatment of tumors in a mammal does not constitute a shift of focus, and is commensurate with the claimed scope of the invention.

Applicants' arguments regarding the combination of oligonucleotide and liposome delivery vehicle are not found persuasive, because the previous office action set forth detailed observations regarding the deficiencies in Examples 12-15 that included the delivery of the combination therapeutic composition. For instance, Example 12 describes the i.v. injection of

oligonucleotides lacking CpG motifs, ranging in size from 10 to 100 nucleotides into mice. The results are presented in Figure 30 and show that activation of $CD8^+/CD69^+$ cells could not be demonstrated with the 10 mer. The results further showed that while some activation of $CD8^+/CD69^+$ cells was detectable for oligonucleotides of 25 and longer lengths, the response was inferior in all cases, compared to a control 20 mer containing two CpG motifs, and contrary to the statement in paragraph [00228] of the instant specification, the responses were not as great as that elicited by the CpG containing oligonucleotide. Further, not only is there no apparent correlation between oligonucleotide size and CD69 activation (as evidenced by a decrease in activation in the 75 mer and 100 mer oligos from that seen with a 50mer), no 20 mer was included in the group of oligonucleotides lacking CpG.

Example 14 describes the i.v. injection into mice of oligonucleotides lacking CpG motifs, wherein the oligonucleotides were either a 10mer or a mixture of 50mer and 75 mer, followed by the isolation and culture of spleen cells for measuring IFNγ release. Here, the results from the 100 mer oligonucleotide were omitted, and IFNγ release was not detectable for the 10 mer, but was present in the mixture of 50mer and 75 mer. As the positive controls in the experiment included plasmid DNA, it is not clear what conclusions may be derived by such non-analogous comparisons. It is noted that the 20mer control oligonucleotide containing two CpG sequences, yielded very little measurable IFNγ release. Applicants' statement that the observation regarding an oligonucleotide containing CpG motifs is irrelevant to the scope of the claims is not on point, because the reference to the oligonucleotide containing CpG motifs is in the context of Example 14, that utilized the CpG containing oligonucleotide as a control.

Example 15 describes the results obtained from an experiment similar to that noted in Example 14, except that IFN-α release was measured. While the 10 mer oligonucleotide did not result in any measurable IFN-α release, the mixture of 50mer and 75 mer oligonucleotides resulted in an increase in IFN-α production over that observed with the CpG oligonucleotide. However, as the oligonucleotides are of different lengths and sequences, no definitive conclusions can be drawn from the experiment. It is further noted that the results from Examples 14 and 15, depicted in Figures 32 and 33 are not directly relevant to the instant claims, as the claims are not directed to a mixture two different oligonucleotides, but rather a single

oligonucleotide. Moreover, none of the examples using oligonucleotides lacking CpG motifs, included the assessment or evaluation of tumors correlate the immune responses generated with any therapeutic effect on any disease or infection. The specification is further silent on the sequence specific effects of the oligos, or the minimum size of an oligonucleotide required to elicit a cytokine response, or whether the cytokine release measured for some of the CpG deficient oligonucleotides would constitute a therapeutically effective amount in the treatment of any disease or infection. The previous office action therefore highlighted the deficiencies in the Examples, and as such analysis is in accord with the *Wands* factors, that include the working examples and the amount of direction or guidance presented, the Examples fail to support an enablement for the claimed invention.

Applicants additionally argue that the documents cited in the rejection do not support an allegation of non-enablement, as both Auf et al. and Vollmer et al. reports results with oligonucleotides in the absence of a liposome delivery vehicle. Such is not persuasive, because the liposome delivery vehicle is simply a means of delivering the oligonucleotides to cells *in vivo*. The fact that Auf et al. employed alternate delivery means such as intratumoral injection for oligonucleotide delivery does not negate their teachings regarding the inability of oligonucleotides lacking CpG motifs (versus those containing) CpG motifs to inhibit tumors, when both types of oligonucleotides were successfully delivered to the tumor. Applicants have not provided any evidence regarding a significant difference in the therapeutic effect of an oligonucleotide composition when delivered by intratumoral or intramuscular injection, versus delivery in a liposome vehicle.

Vollmer et al. employed intramuscular injection to deliver oligonucleotides *in vivo*, and showed that oligodeoxynucleotides lacking CpG dinucleotides are less potent than CpG ODN and the mechanism by which they stimulate leucocytes is not understood. Applicants argue that Vollmer et al.'s description of a "new" sequence motif that has immune stimulatory activity is consistent with the instant invention in that the "new" motif also lacks a CpG motif, that should support enablement for the claimed invention because it would be expected to elicit a systemic, non-antigen specific immune response when used with a liposome delivery vehicle. Such is not found persuasive, because the observation of Vollmer et al. regarding a new sequence motif supports the grounds of rejection set forth in the previous office action, because it is consistent

with the requirement for a specific sequence in an oligonucleotide in eliciting an immune response, rather than a general lack of a CpG motif. Vollmer et al. state: "Without a phosphorothioate backbone, the presence of CpG dinucleotides becomes more critical for immune stimulation. Only a few reports describe immune stimulation mediated by phosphodiester non-CpG ODN, and they had usually to be added at extremely high concentrations" (first column, p. 221). Also observing: "non-CpG ODN induce Th2-dominated immune responses in contrast to Th1-biased effects seen with CpG ODN...as non-CpG ODN appear to lack one of the most important features of CpG ODN, the efficient stimulation of Th1-like cytokines, including type I interferons." (first column, p. 221).

Thus, the rejection of the claims is maintained for reasons of record, and the foregoing commentary.

Conclusion

Claims 1-22 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on **(571) 272-0739**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

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